REMARKS

Claims 1, 8-10, 19, 21-25, 27, 28, 31-33, and 36-39 have been amended. Support for the claims as amended can be found in the claims as originally filed and in the specification at page 2, lines 21-25.

Claims 7, 11, and 20 are canceled herein. Claims 6, 16, and 26 were canceled previously. Such cancellation is without prejudice to further prosecution of these claims in one or more continuing applications.

Claims 40-41 have been added herein.

Claims 1-5, 8-10, 12-15, 17-19, 21-25, and 27-41 are pending. Favorable reconsideration is respectfully requested.

The following remarks address the issues presented in the Office Action in order of their appearance.

Rejection of Claims 1-5, 7-15, 17-25, and 27-39 Under 35 USC §112, First Paragraph (Written Description):

This rejection is respectfully traversed.

With regard to the nature of the fluorophore, the Office has taken the position that the dansylation reaction described in the specification is insufficient to satisfy the written description requirement because "modifying any ACP protein by different fluorophores involving different reactions is not representative of the single described species." Office Action, page 6, second full paragraph. Applicants traverse this portion of the rejection on two grounds: 1) the Office's conclusion is wholly unsupported by any evidence that analogous labeling reactions cannot be performed using well-known reactions; and 2) the Exhibits submitted in Applicants' prior response clearly establish that the dansylation reaction described in the specification is representative for an enormous host of different types of commercially available fluorophores.

Regarding the first grounds, the Office has failed to articulate *why* the dansylation reaction described in the specification is not representative. The Office has simply concluded that it is not, apparently without any examination of the supporting

documentation submitted in Applicants' prior response. For this reason, Applicants respectfully submit that this rejection is improper on its face.

Regarding the second grounds, Applicants submit that the dansylation reaction described in the specification is representative and can be extended to affix any number of commercially-available fluorphores to a tyrosine residue, **in the exact same fashion** as described in the specification.

The specification presents a general method to attach a non-radioactive probe to an ACP having a tyrosine residue. See page 9, lines 10-15, and page 11, line 12, to page 12, line 22 of the specification. By introducing an amine functionality having a unique pKa value to the tyrosine residue, simple acid-base chemistry can be used to affix a label to the reactive amine moiety. Because of the unique pKa of the introduced amine group (4.75), the pH of the reaction buffer controls the reactivity of that specific amine group. The reaction is thus general and will work with any ACP having a tyrosine group.

The reaction exemplified in the specification is very simple and representative of a reaction between a salt and a primary amine. A dansyl chloride is reacted with an tyrosine residue of the ACP that has been modified to include a amino moiety. See page 11, line 12, to page 13, line 9. The dansylation reaction itself is nothing more complicated than the reaction of a salt with an amino group. Moreover, the specification clearly notes potential "glitches" with the reaction. For example, the specification notes that the reaction can yield both mono- and di-dansylated products. However, the specification also clearly explains how to separate the mono-substituted produce from the di-substituted product. See page 13, first paragraph.

This reaction is **exactly analogous** to reacting any other salt or ester with a primary amine. In this regard, please see Tables 1.2 and 1.3 of Exhibit 3 as submitted in Applicant's prior response. Table 1.2 lists a host of dyes, including the Alexa Fluor Dyes 350, 405, 430, 488, 500, 514, 532, 546, 555, 568, 594, 610, 633, 647, 660, 680, 700, and 750, as well as Marina Blue, Pacific Blue, Fluorescein, Oregon Green, tetramethylrhodamine, Rhodamine Red, and Texas Red, that are available in the form of succinimidyl esters. These succinimidyl esters react with an amine modified tyrosine

residue in the same fashion and the danysl chloride reaction described in the specification. In particular, see the right-hand column of Table 1.3 of Exhibit 3, which describes these Molecular Probes-brand kits: "The reactive dye has a succinimidyl ester moiety that reacts efficiently with primary amines of proteins to form stable dye-protein conjugates."

Thus, the information provided by Molecular Probes (just one commercial supplier among a great many) is quite clear. Molecular Probes provides a truly astounding variety of fluorophores in the form of succinimidyl esters, all of which will react readily with primary amines. One of skill in the art can readily access this information and purchase any number of suitable kits from Molecular Probes (and many other suppliers as well). The person of ordinary skill can successfully label the amino-modified tyrosine as described in the present specification using, for example, the succinimidyl ester dyes from Molecular Probes, using the exact same protocol as described in the specification. Thus, the dansylation reaction described in the specification is submitted as being clearly representative of any type of labeling reaction involving a primary amine and a salt or ester.

Applicants' prior submission makes it clear that it is well known how to affix a very large number of fluorophores to an amino-modified tyrosine. A very large number of these fluorphores are available commercially, as evidenced by the Molecular Probes literature submitted to the Office in Applicants' prior response. It is well-settled law that what is well-known in the art is best omitted from the specification. MPEP §2164.08 and *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Thus, having provided a representative example of how to modify a tyrosine residue to include an amino group, and how to react a dansyl chloride with that amino group, Applicants have provided a general approach that can be used to affix a huge variety of fluorophores to the ACP.

Regarding the nature of the ACP, this rejection has been overcome, in part, by amendment to the claims, and is, in part, respectfully traversed. The claims have been amended to recite that the ACP must have a tyrosine residue. In this regard, Applicants again refer to the specification at page 6, line 15, to page 7, line 4:

> As used herein, the term acyl carrier protein (ACP) denotes any acyl carrier protein, derived from any source whatsoever (naturally-derived, semi-synthetic, fully-synthetic) that includes at least one tyrosine residue. In many ACPs, a tyrosine residue is located in a position near to the C-terminal, as is the case with *E. coli* ACP. In other cases, a tyrosine residue is located near to the conserved serine residue that acts as the site of phosphopantetheinylation. In a limited number of cases, tyrosine residues are present in both locations. A tyrosine residue is found in the ACPs of every bacterial genus that has an entry in GenBank. Thus, it is very likely that other organisms not presently cataloged within GenBank will also have ACPs that include a suitable tyrosine residue. Organisms cataloged with GenBank that have an ACP having at least one tyrosine residue (and are thus ACPs that can be used in the present invention) include: *Bacillus*, *Clostridium*, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Mycobacterium*, *Mycoplasma pneumonia*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Shigella dysenteria*, *Streptococcus pyogenes*, *Treponema pallidum*, and *Vibrio cholerae*. Other organisms that are not cataloged within GenBank, but that are believed to have ACPs that contain at least one tyrosine residue include, without limitation: *Borellia burgdorferi*, *Bortedella*, *Brucella*, *Corynebacterium*, *Listeria monocytogenes*, *Staphylococcus*, and *Yersinia pestis*.
>
> Thus, any ACP isolated from or derived from any of these sources and modified to contain a non-radioactive label as described herein, falls within the scope of the present invention.

The specification clearly includes a rather extensive list of potential sources for suitable ACPs. Thus, a person of ordinary skill in the art has been provided an exemplary list of ACPs, as well as the name of a publicly-accessible database (GenBank) where additional ACPs can be found. Any number of ACP proteins can be found by searching GenBank, a database that is accessible to the public without cost and is fully searchable.

As noted in Applicants' prior response, ACPs are a remarkably conserved class of proteins. Thus, in terms of satisfying the written description requirement, Exhibit 1 of Applicants' prior response (which explicitly states that the amino acid sequence of ACPs are conserved to a "high degree,") and the large list of ACP sources quoted above, clearly provides amply written description of the sources of ACPs that can be used in the present invention. Coupled with the generality of the dansylation reaction, as noted above, the specification clearly conveys sufficient written information to indicate that the Applicants' had possession of the invention as broadly as it is now claimed.

The Office provided no comment regarding the fact that ACPs **are** highly conserved. Applicants provided third party, independent evidence clearly establishing that the genus of ACPs **is not** variable. The genus "ACP" is, as evidenced by Exhibits 1 and 2 of Applicants' prior response, **highly conserved and invariable**.

In response, the Office continues to assert, with absolutely no support whatsoever, that ACPs are "a large variable genus." See the Office Action, page 4, line 2. If ACPs are a "large variable genus" as the Office asserts, Applicants request that the Office support its conclusion by way of scientific evidence. In their prior response, Applicants provided two independent papers that clearly establish that ACPs are **highly conserved** and **invariable**. In particular, the Office made no comment on Applicants' Exhibit 2, which demonstrated a remarkable conservation of amino acid sequence between ACPs isolated from Haemophilus, Vibrio, Leptospiraacyl, Lactobacillus, and Mycoplasma. In the absence of any countervailing evidence, the Office's continued insistence on this point is without merit.

In conclusion, Applicants have included in the specification very extensive lists of sources for suitable ACPs, as well as suitable non-radioactive labels that can be used in the invention, along with a representative synthesis for affixing the label to the ACP. Having done so, Applicants respectfully submit that the written description requirement of 35 USC §112, first paragraph, have been satisfied.

Applicants therefore submit that the rejection of Claims 1-5, 7-15, 17-25, and 27-39 under §112, first paragraph (written description) is untenable. Withdrawal of the same is respectfully requested.

Rejection of Claims 8-9, 17-18, 27-28, 32-37, and 38 Under 35 USC §112, Second Paragraph:

Regarding Claim 19, the errant extra period (.) has been removed from the claim.

Applicants acknowledge the Office's position with respect to referring to hyperlinks in a patent application specification. However, with respect to their IDS of June 23, 2004, Applicants were not attempting to incorporate a hyperlink. Applicants were simply listing

the origin of the **paper** documents that were duly submitted for consideration. Specifically, note that in the 6th and 7th entries of their IDS submitted June 23, 2004, Applicants listed the number of pages of these two papers so that the Office could easily identify the corresponding papers. Note that **paper copies** of these documents were submitted to the Office in Applicants' supplemental IDS. In short, there was no other practical way to identify these paper submissions other than by listing the web pages from which they were accessed. Applicants thus respectfully request that the 6th and 7th entries of their IDS filed June 23, 2004, which correspond to hard copy documents submitted to the Office, be made of record, considered on the merits, and listed on the "References Cited" field on any patent that issues from this application.

The remainder of this rejection is respectfully traversed because the Office has not shown by way of objective evidence or sound scientific reasoning that fluorophores such as fluorescein, rhodamine, FITC, TRITC, and/or Texas Red **cannot** label a tyrosine residue using the exemplary disclosed in the specification (and described in detail in the prior section). In short, if the Office doubts the operability of the present invention, the Office must support its conclusion with something more than a wholly unsupported conclusion.

In short, in making this rejection, the Office states, without further elaboration, that "Fluorophores such as fluorescein, rhodamine, fluorescein isothiocyanate (FITC) or tetramethylrhodamine isothiocyanate (TRITC) & Texas Red, are not known to label tyrosine of the protein by covalent bonding." No further discussion is provided. Applicants therefore respectfully submit that this rejection is *prima facie* improper. The Office simply has not provided any objective support for its ultimate conclusion. Moreover, and as discussed below, the Office's conclusion is flatly contradicted by the Molecular Probes product literature submitted in Applicants' prior response.

This rejection is further traversed because the Office has simultaneously asserted, in rejecting several of these same claims as being obvious under 103(a), that reactions and protocols to perform these exact same reactions are "well known," "widely available," and are taught in the prior art with "a resonable expectation of success." Applicants respectfully submit that the Office **cannot** have it both ways. Either the documents

submitted in Applicants' prior IDS prove what is well-known in the art (and thus need not be included in Applicants' specification) or they do not.

On this issue, Applicants have been clear and consistent. The specification as filed, as well as the knowledge that can be attributed to one of skill in the art, clearly teaches how to affix a fluorophore label to a protein substrate. If the Office agrees with this position, than the present rejection under 112 is fatally flawed. If the Office disagrees with this position, then the Office's rejection under 103(a) (discussed below) is fatally flawed. (Applicants note that the rejection under 103(a) is improper on other grounds as well, namely the combination does not teach or suggest the invention as claimed.)

In any event, the specification presents a general method to attach a non-radioactive probe to an ACP having a tyrosine residue. See page 9, lines 10-15, and page 11, line 12, to page 12, line 22 of the specification. By introducing an amine functionality having a unique pKa value to the tyrosine residue, simple acid-base chemistry can be used to affix a label to the reactive amine moiety. Because of the unique pKa of the introduced amine group (4.75), the pH of the reaction buffer controls the reactivity of that specific amine group. The reaction is thus general and will work with any ACP having a tyrosine group.

The reaction exemplified in the specification is very simple and representative of a reaction between a salt and a primary amine. A dansyl chloride is reacted with an tyrosine residue of the ACP that has been modified to include a amino moiety. See page 11, line 12, to page 13, line 9. The dansylation reaction itself is nothing more complicated than the reaction of a salt with an amino group. Moreover, the specification clearly notes potential "glitches" with the reaction. For example, the specification notes that the reaction can yield both mono- and di-dansylated products. However, the specification also clearly explains how to separate the mono-substituted produce from the di-substituted product. See page 13, first paragraph.

This reaction is exactly analogous to reacting any other salt or ester with a primary amine. In this regard, please see Tables 1.2 and 1.3 of Exhibit 3 as submitted in Applicant's prior response. Table 1.2 lists a host of dyes, including the Alexa Fluor Dyes 350, 405, 430, 488, 500, 514, 532, 546, 555, 568, 594, 610, 633, 647, 660, 680, 700,

and 750, as well as Marina Blue, Pacific Blue, Fluorescein, Oregon Green, tetramethylrhodamine, Rhodamine Red, and Texas Red, that are available in the form of succinimidyl esters. These succinimidyl esters react with an amine modified tyrosine residue in the same fashion and the danysl chloride reaction described in the specification. In particular, see the right-hand column of Table 1.3 of Exhibit 3, which describes these Molecular Probes-brand kits: "The reactive dye has a succinimidyl ester moiety that reacts efficiently with primary amines of proteins to form stable dye-protein conjugates."

Thus, the information provided by Molecular Probes is crystal clear. Molecular Probes provides a truly astounding variety of fluorophores in the form of succinimidyl esters, all of which will react readily with primary amines. One of skill in the art can readily access this information and purchase any number of suitable kits from Molecular Probes (and many other suppliers as well). The person of ordinary skill can successfully label the amino-modified tyrosine as described in the present specification using, for example, the succinimidyl ester dyes from Molecular Probes, using the exact same protocol as described in the specification. Thus, the dansylation reaction described in the specification is submitted as being clearly representative of any type of labeling reaction involving a primary amine and a salt or ester.

Applicants therefore respectfully submit that the rejection of Claims 8-9, 17-18, 27-28, 32-37, and 38 under 35 USC §112, second paragraph, is improper. Withdrawal of the same is respectfully requested.

Rejection of Claims 1-3, 7-10, and 17-18 Under 35 USC §102(b) Over McAllister et al. (Sept. 17-20, 2000) *Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy* 40:225:

This rejection is believed to have been overcome, in part, by appropriate amendment to the claims, and is, in part, respectfully traversed.

The relevant passage of the McAllister et al. abstract states :

> To replace [a ^{3}H-based] assay, we synthesized fluorescein-CoA, measured AcpS activity using the fluorescein-CoA, and subsequently verified the incorporation of the fluorescein-CoA into apo-ACP by mass spectrometry. When fluorescein-CoA was used as a substrate... the incorporation of fluorescein-labeled phosphopantetheine onto [*sic*] apo-ACP was monitored by a fluorImager.

Note that in the McAllister et al. assay, the label is attached to the AcpS **substrate**, co-enzyme A ("CoA"). The CoA is then incorporated into the apo-APC as the phosphopantetheine prosthetic group (to thereby yield holo-ACP). Note that CoA and the phosphopantetheine prosthetic group are closely related (see Exhibit A, attached hereto and incorporated herein). As noted in Applicants' specification at page 1, lines 15-20, the phosphopantetheine prosthetic group is attached to a conserved serine residue in apo-ACP.

Thus, in McAllister et al's assay, the fluorescein label is **never** attached to an apo-ACP. Apo-ACP lacks the phosphopantetheine prosthetic group. McAllister et al., however, attach their label to CoA, a precursor to the phosphopantetheine prosthetic group. McAllister et al. then use the enzymatic action of AcpS to attach the labeled prosthetic group to apo-ACP, **thereby yielding labeled holo-ACP**. Thus, McAllister et al. describe **a holo-ACP** wherein a fluorescein is attached to the phosphopantetheine prosthetic group.

As applied to Claim 7, this rejection has been rendered moot by cancellation of the claim.

As applied to Claims 1-3, 8, and 9, this rejection is believed to have been overcome by appropriate amendment to the claims. Specifically, as amended, Claim 1 requires that the ACP contain at least one tyrosine residue and that the label be bonded to that tyrosine residue. Claims 2, 3, 8, and 9 depend directly from Claim 1 and therefore also incorporate this limitation. Because McAllister et al. do not describe such an arrangement, this portion of the rejection is believed to have been overcome.

Thus, as applied to Claims 10, 17, and 18, this rejection is respectfully traversed. Claim 10 as originally submitted and as amended herein requires that the fluorophore be covalently bonded to a tyrosine residue of the ACP. Claims 17 and 18 depend from Claim

10. Because McAllister et al. do not describe an ACP having a fluorophore attached to the protein via a tyrosine residue of ACP, this portion of the rejection is clearly improper.

In light of amendment to the claims and the above comments, Applicants respectfully submit that the rejection of Claims 1-3, 7-10, and 17-18 under §102(b) over McAllister et al. is no longer tenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 4-5, 11-15, 19-25, and 27-39 Under 35 USC §103(a) Over McAllister et al., in View of Abita et al. (1971) *Eur. J. Biochem.* 23:412-420, and Dawson et al. "Data for Biochemical Research," 3rd Ed. copy. 1986, and the Molecular Probes technical guides submitted in Applicants' IDS filed June 23, 2004:

As a procedural matter, this rejection is respectfully traversed because the Office is attempting to have its cake and eat it too. As noted earlier with respect to the rejections under §112, knowledge that is well known to a person of skill in the art is well known for all purposes. The Office is not at liberty to reject the present claims on the assertion that one of skill in the art would have to exercise undue experimentation to affix a fluorophore other than dansyl to a tyrosine residue of a protein, and then simultaneously to reject the claims as being obvious on the assertion that it would be obvious to do the exact same thing using reagents that are "well known and widely available." See page 10 of the Office Action, 2nd full paragraph.

Thus, Applicants traverse this rejection because the Office has failed to establish a *prima facie* case of obviousness because the Office has adopted irreconcilable interpretations of the prior art. The Office has explicitly taken the position that "fluorescein, rhodamine, FITC, TRITC and Texas Red **are not known... to label tyrosine of the protein or covalently [bond] to the tyrosine as claimed**." See the Office Action at page 4, lines 14-17. If this is the case, how then can the references submitted in Applicants' prior IDS simultaneously enable reactions which the Office has already stated "are not known."?

In addition to the Office's inconsistent assertions regarding the scope of the prior art, this rejection is also traversed on the substantive merits because the **combination** of references in no way teaches or suggest arriving at either the claimed method or the corresponding kits as they are positively recited in the present claims.

Specifically, as noted in the prior section, in McAllister et al's assay, the fluorescein label is **never** attached to an apo-ACP. The McAllister et al. reference fails entirely to disclose, suggest, teach, or motivate making a labeled apo-ACP of any sort. Apo-ACP lacks the phosphopantetheine prosthetic group. McAllister et al., however, attach their label to CoA, a precursor to the phosphopantetheine prosthetic group. McAllister et al. then use the enzymatic action of AcpS to attach the labeled prosthetic group to apo-ACP, **thereby yielding labeled holo-ACP**. Thus, McAllister et al. describe **a holo-ACP** wherein a fluorescein is attached to the phosphopantetheine prosthetic group.

Thus, McAllister et al. **do not** describe any type of labeled apo-ACP. McAllister also **do not** describe any type of labeled acyl-ACP. McAllister also do not describe any type of ACP (apo-, holo-, or acyl) that has a label attached to the ACP via a tyrosine residue of the ACP.

Thus, when the McAllister et al. assay is **combined** with any of the secondary references, the resulting **combination** is a labeled CoA substrate as taught by McAllister et al., wherein the label is any of those taught in the Molecular Probes technical guides or Dawson et al. (*e.g.*, rhodamine, FITC, Texas Red, etc.). The labeled CoA substrate is then reacted with the apo-ACP of Abita et al. in the presence of AcpS (as taught by McAllister), to yield a holo-ACP having a labeled phosphopantethienyl prosthetic group. Neither the resulting labeled holo-ACP product taught by the combination, nor the process to make the labeled holo-ACP taught by combination, nor any corresponding kit taught by the combination are the same as the positively recited products, processes, and kits of the present claims.

Addressing these in order, all of the presently claimed ACPs require a fluorophore bonded to a tyrosine residue of the ACP. The combined references do not describe this approach because McAllister affix a label not to a tyrosine residue of the ACP, but to the

CoA substrate that ultimately becomes the prosthetic group of holo-ACP. Thus, the combination of applied references teaches nothing more than a holo-ACP that is labeled at the prosthetic group. And the prosthetic group is attached to the ACP via a conserved serine residue, not a tyrosine residue. See the present specification at page 1, lines 15-17. The combination does not teach or suggest labeled apo-ACPs or acyl-ACPs.

Regarding the methods recited in Claims 29 and 30, the combination of references clearly fails to teach or suggest the positively recited elements of these two claims. These claims positively recite modifying a tyrosine residue of the ACP to incorporate an amino moiety into the tyrosine residue. A non-radioactive label is then covalently bonded to the amino moiety previously incorporated into the tyrosine residue of the ACP. As recited in Claim 29, the modified apo-ACP (**not** the modified CoA, as taught by McAllister) is then reacted with AcpS to yield labeled holo-ACP. Claim 30 further requires that the labeled holo-ACP by acylated to yield labeled acyl-ACP. **None** of the steps are described by the **combined** references.

The same can be said for the kits recited in the present claims. By the Office's own admission, the Abita et al. reference **does not** teach the labeling of the ACP described therein. See the bottom of page 9 of the Office Action. Nor do any of the other secondary references cited in support of this rejection. That leaves only the McAllister et al. reference, which teaches only that the CoA substrate be labeled, **not** the ACP protein itself. Thus, when the references are **combined**, the only kit that can result is a kit containing either unlabeled apo-ACP (as taught by Abita et al.) and labeled CoA (as taught by McAllister et al, and using any of the labels described in Dawson et al. or the Molecular Probes technical guides). But that is not what is required by the positive language of the present kit claims.

Another alternative is to have a kit containing holo-ACP (Abita et al.) which is labeled as described by McAllister et al., using one of the labels described in Dawson et al. or the Molecular Probes literature. However, this combination still places the label on on the phosphopantetheinyl group of the holo-ACP. As noted above, the phosphopantetheinyl group is attached to a conserved serine residue of the ACP, not a

tyrosine residue as required by the present claims. Thus, the **combination** of reference still fails to teach or describe the positively claimed kits.

In light of the above amendment and the foregoing remarks, Applicants submit that the rejection of Claims 4-5, 11-15, 19-25, and 27-39 under§103(a) over McAllister et al., in view of Abita et al., and Dawson et al., and the Molecular Probes technical guides submitted in Applicants' IDS filed June 23, 2004 is improper. Withdrawal of the same is respectfully requested.

CONCLUSION

In light of the above amendment, remarks, and the Rule 131/132 Declaration filed herewith, Applicants respectfully submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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The *synthesis of coenzyme A* (CoA) in animals starts with the phosphorylation of *pantothenate* (Figure 22-26). Pantothenate is required in the diet of animals, whereas it is synthesized by plants and microorganisms. A peptide bond is formed between the carboxyl group of 4′-phosphopantothenate and the amino group of cysteine. The carboxyl group of the cysteine moiety is lost, which results in *4′-phosphopantotheine.* The AMP moiety of ATP is then transferred to this intermediate to form *dephosphocoenzyme A*. Finally, phosphorylation of its 3′-hydroxyl group yields coenzyme A.

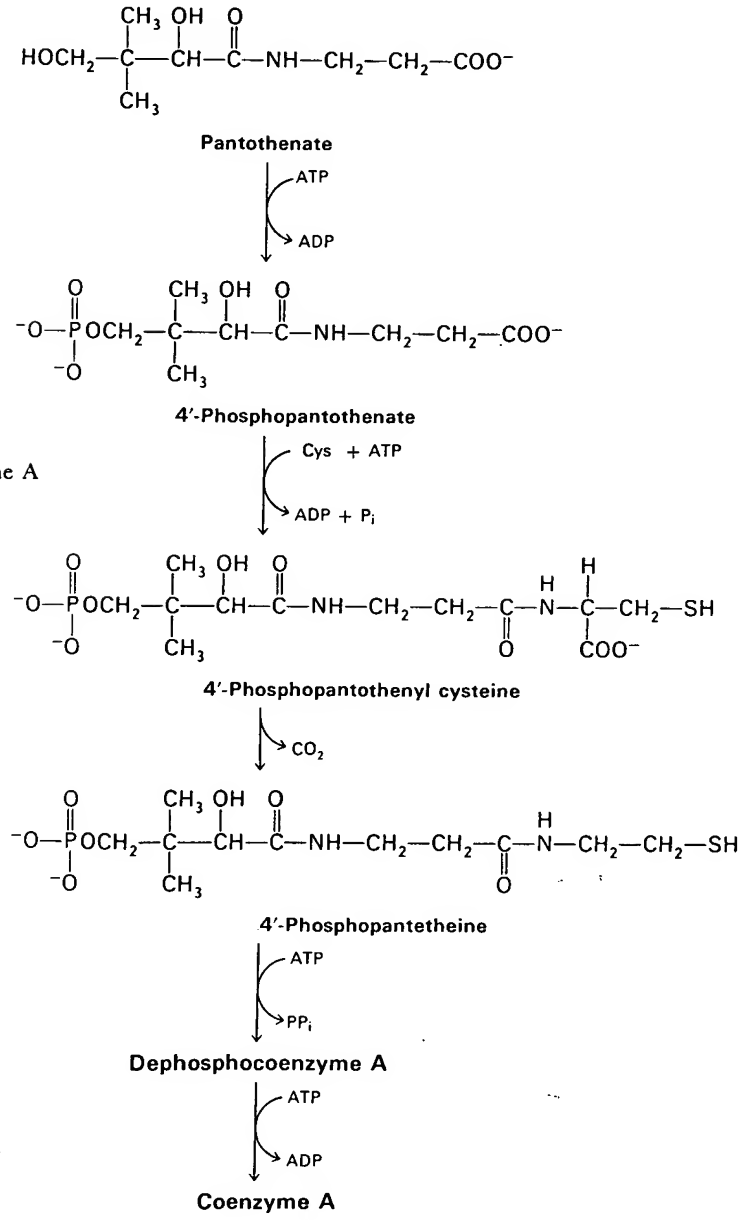

Figure 22-26
Synthesis of coenzyme A from pantothenate.